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The effect of physical exercise on cerebral blood flow in Alzheimer's disease

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ABSTRACT

In recent years there has been an increasing focus on the relation between cerebrovascular health, physical exercise and Alzheimer's disease. The aim of the current study was to determine the effect of moderate-to-high-intensity aerobic exercise on cerebral blood flow in patients with mild to moderate Alzheimer's disease. Fifty-one patients were randomized to either usual care or moderate-to-high intensity aerobic exercise for 16 weeks. Exercise had no consistent effect on whole brain or regional cerebral blood flow. Sixteen weeks of exercise are, therefore, not sufficient to produce a consistent increase in cerebral blood flow in a relatively small sample of Alzheimer's patients.

1. Introduction

Alzheimer's disease (AD) poses a large burden on our increasingly aging population. In addition to its characteristic Amyloid β and Tau pathology, Alzheimer's disease is also marked by changes in cerebral blood flow (CBF) as AD patients show a 40% decrease in global blood flow compared to healthy controls (Austin et al., 2011). A decreased CBF already occurs in individuals with mild cognitive impairment (MCI) before their transition to AD (Binnewijzend et al., 2013). Certain regions appear to show a particularly decreased CBF in AD, including the precuneus, hippocampus, and posterior cingulate gyrus (Austin et al., 2011; Binnewijzend et al., 2013; van Osch and M, 2011). Interestingly, local hyperperfusion has also been reported despite a global CBF reduction, which has been hypothesized to be a compensatory mechanism (Austin et al., 2011).

CBF also provides a method to assess disease severity, as it is associated with cognitive functioning even within a group of AD patients (Eggermont et al., 2006; Tosun et al., 2016). Moreover, a lower CBF as measured with ASL MRI is related to the rate of future cognitive decline in both healthy elderly individuals and AD patients (Benedictus et al.,

2017; Chao et al., 2010; De Vis et al., n.d.; Wolters et al., 2017; Xekardaki et al., 2014). These findings mark CBF as a potential target for interventions. Interestingly, in healthy individuals the association between age and gray matter CBF is mediated by cardiorespiratory fitness (Zimmerman et al., 2014). As well, aerobic exercise has been shown to both mitigate the effect of age on CBF and improve cognition in healthy individuals (Ainslie et al., 2008; Lucas et al., 2012). Thereby, increasing cardiorespiratory fitness may aid in preventing or slowing pathological cognitive decline by increasing CBF. In earlier studies regular exercise was reported to improve cognitive function and lowering the risk of future MCI and dementia (Ahlskog et al., 2011). As well, various studies have shown a beneficial effect of physical exercise on cognition in individuals with dementia (Groot et al., 2016).

The aim of the current study was to determine the effect of moderate-to-high-intensity aerobic exercise on cerebral blood flow in patients with Alzheimer's disease (AD).

2. Materials and methods

The ADEX study (ClinicalTrials.gov no.: [NCT01681602](https://clinicaltrials.gov/ct2/show/study?term=NCT01681602)) is a

Abbreviations: ACC, anterior cingulate cortex; AD, Alzheimer's disease; CBF, cerebral blood flow; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; PCC, posterior cingulate gyrus; SPG, superior parietal gyrus

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multicenter, single-blind, randomized, controlled trial to investigate whether a supervised aerobic exercise program could ameliorate symptoms of AD. The ADEX trial was approved by the The Committees of Biomedical Research Ethics for the Capital Region (Protocol no.: H-3-2011-128) and by the Danish Data Protection Agency (j.no.: 30-0718).

2.1. Participants

A total of 200 patients with mild to moderate AD were randomized to either an exercise group or to a control group (usual care). A subgroup of patients underwent brain MRI at baseline and at 16 weeks (Hoffmann et al., 2013). All participants recruited at the main three study centers site were asked to participate in the MRI-substudy. Among the inclusion criteria are a clinical diagnosis of probable AD, a Mini Mental State Examination (MMSE) score of > 19 (Folstein et al., 1975), age 50–90 years, stable dose of anti-dementia or mood stabilizing medication. The exclusion criteria include contraindications for physical activity, participation in high intensity physical exercise $> 2 \times$ per week, severe psychiatric disease or alcohol abuse within last 2 years. The inclusion criteria were described in detail earlier (Hoffmann et al., 2013).

2.2. Intervention

The exercise group underwent 60 min exercise sessions, three times a week for 16 weeks. All exercise sessions were supervised. The first four weeks consisted of adaptation training for which participants received an *introduction to exercise* session once week, and two exercise sessions a week focusing on building strength (mostly in the legs). The exercise sessions in the subsequent 12 weeks consisted of moderate-to-high intensity aerobic exercise. The intensity of the exercises were adjusted per individual participant to target 70–80% of the heart rate reserve. The exercises were performed on a cross trainer, bicycle and treadmill.

The control group received care as usual.

2.3. Imaging protocol

All imaging was performed on a 3T (Trio, Siemens, Erlangen, Germany). The imaging protocol included a T_1 -weighed magnetization-prepared rapid gradient echo (MPRAGE): TR 1550 ms, TE 3.04 ms, FOV 256×256 , 192 slices. A Pulsed Arterial Spin Labeling (PASL) sequence was used to obtain quantitative perfusion measurements with a flow-sensitive alternating inversion recovery (FAIR) labeling scheme, 3D gradient-and-spin-echo (GRASE) multishot readout. PASL provides a method to non-invasively measure cerebral perfusion through the labeling of blood water at the neck region. Images are acquired after a predefined post label delay when the labeled protons have reached the tissue. The parameters of the PASL sequence were: TR 3400 ms, TE 19 ms, TI 2000 ms, FOV 320×160 , matrix 64×32 , 26 slices, voxel size $5 \times 5 \times 4 \text{ mm}^3$. A Fluid Attenuated Inversion Recovery (FLAIR) sequence was used to calculate white matter hyperintensity (WMH volume). The FLAIR sequence parameters were: TR = 6000 ms, TE = 353 ms, TI = 2200 ms, FOV $256 \times 220 \times 192$.

2.4. Data processing

To obtain quantitative perfusion maps, the obtained ASL images were processed using IDL 6.1 for Windows (ITT Visual Information Solutions, Boulder, C.O., U.S.A.). The quantitative perfusion maps were registered to the T_1 -weighted images that were segmented using FreeSurfer (<http://freesurfer.net/fswiki/FreeSurferWiki>). Whole brain CBF was calculated, and five, bilateral regions were selected known to be involved in AD related perfusion changes: the frontal lobe, anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), superior parietal gyrus (SPG) and the precuneus (Austin et al., 2011; Binnewijzend

et al., 2013; van Osch and M, 2011). The T_1 -weighed images were segmented with FreeSurfer. The PASL images were linearly registered to the MPRAGE space to select the areas for regional CBF analysis (<https://surfer.nmr.mgh.harvard.edu/fswiki/>). The absolute change in CBF ($\text{CBF}_{\text{follow-up}} - \text{CBF}_{\text{baseline}}$) and relative change in CBF ($(\text{CBF}_{\text{follow-up}} - \text{CBF}_{\text{baseline}}) / \text{CBF}_{\text{baseline}} * 100\%$) were calculated. Areas clearly hyperintense relative to surrounding white matter on both FLAIR and T_2 -weighted images were delineated to obtain WMH volume. Local thresholding was applied and WMH volumes for the whole brain were quantified automatically using the Jim image analysis package, Version 6.0, (Xinapse Systems Ltd., Northants, UK, www.xinapse.com). Visual identification and delineation was carried out by a single trained rater blinded to clinical information.

2.5. Cognitive and physical outcome measures

The Mini Mental State Examination (MMSE) was administrated at baseline and at 16-week follow-up. VO_2 peak (ml/kg/min) was recorded at both time points using direct breath-by-breath cardiopulmonary exercise test (CPET) performed on a graded cycle ergometer. Indirect calorimetry and expired gases were assembled and analyzed using a metabolic measurement system (Jaeger, Master Screen CPX vers. 5.21, Cardinal Health, Germany)). VO_2 peak was measured at self-termination of the test and maximal effort was set at $\text{RER} \geq 1.05$. (Sobol et al., 2016). VO_2 peak was obtained from 34 participants.

2.6. Statistical analysis

Statistical analysis was carried out with R (R Foundation for Statistical Computing, Vienna, Austria). Outliers were defined conservatively as values above 4 median absolute deviations (MADs), and they were removed from the results. Given the non-normal distribution, the non-parametric statistical tests Wilcoxon rank-sum test, Wilcoxon signed-rank test and Spearman's correlation were used. Bonferroni correction was used for multiple comparisons.

3. Results

Fifty-one patients were included in the analysis (Fig. 1). Baseline characteristics were similar between the exercise and control group (Table 1). The similarity of the two study arms was also reflected in the baseline whole brain CBF: the median CBF was 39 (interquartile range

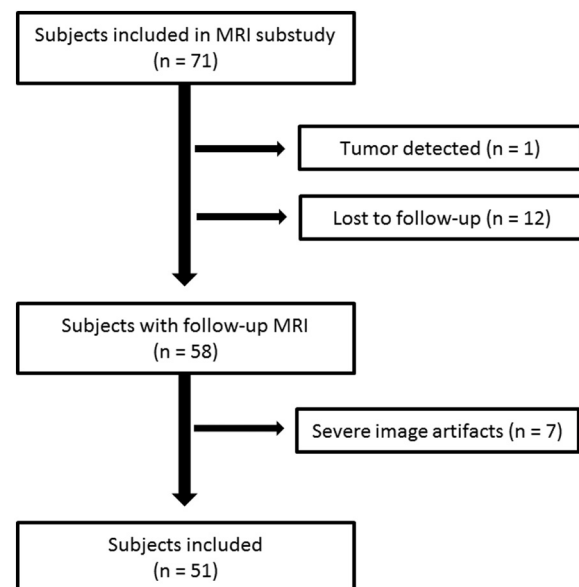


Fig. 1. Flowchart.

Table 1
Baseline characteristics.

	Exercise group (n = 27)	Control group (n = 24)	Difference between study groups
Age (mean \pm sd)	68 \pm 7	69 \pm 7	n.s.
Sex (female, %)	37%	41%	n.s.
MMSE (mean \pm sd)	25 \pm 3	25 \pm 3	n.s.
WMH (mm ³)	3.5 \pm 6.5	4.8 \pm 6.1	n.s.
Hypertension	10 (37%)	11 (46%)	n.s.

MMSE = mini mental state examination; WMH = white matter hyperintensities; n.s. = not significant.

(IQR) 32–42) ml/100 g/min and 36 (IQR 31–43) for the control and intervention group, respectively.

After the 16-week intervention the median difference in whole brain CBF was -6 (IQR -1 – 3) ml/100/min for the control group and -4 (IQR 0 – 3) ml/100/min for the intervention group. The change in CBF over the study period did not differ between the control group subjects and exercise group subjects ($P > 0.05$, Fig. 2, Table 2). The effect of exercise on cardiorespiratory fitness was reflected in the VO₂ peak. There was no difference in the VO₂ peak at baseline between the exercise and control arm (24 mL/min/kg (IQR 19–29) and 24 mL/min/kg (IQR 23–29, respectively)), whereas the VO₂ peak was increased after 16 weeks in the exercise group ($p < 0.01$), but stable in the control group (27 mL/min/kg (IQR 21–32) compared to 25 mL/min/kg (IQR 23–19)).

4. Discussion

Sixteen weeks of moderate-to-high intensity aerobic exercise did not have an effect on.

cerebral blood flow in a group of patients with mild to moderate Alzheimer's disease. The effect of the exercise intervention on cardiorespiratory fitness (VO₂ peak) did not translate to CBF. This was observed for whole brain as well as for regional CBF in the frontal precuneus. The absence of detectable changes induced by the 16-week exercise intervention is in line with results from other modalities in this study (Hoffmann et al., 2016; Sobol et al., 2016; Steen Jensen et al., 2016). Yet, an effect of exercise has been reported on several neuropsychological and physical function tests in the ADEX trial (Hoffmann et al., 2016; Sobol et al., 2016).

These results demonstrate that although the exercise regime as used in the ADEX trial can positively affect cognition in individuals with Alzheimer's disease, the effect is not reflected in CBF changes. The intensity of the physical exercise program was in line with guidelines for older adults (Nelson et al., 2007; Paterson and Warburton, 2010). A strength of this study was the close monitoring of each participant during each exercise session, including individual adjustment to target 70–80% of the heart rate reserve. As such, adherence and proper execution of the exercise program was monitored. A limitation of the study is the length of the intervention, as possibly a longer trial duration would yield different results. Still the optimal duration for such a trial is unknown, and effect of the exercise on cognition in the total population indicates that the length was appropriate for cognitive changes (Hoffmann et al., 2016). Several clinically relevant ROIs were

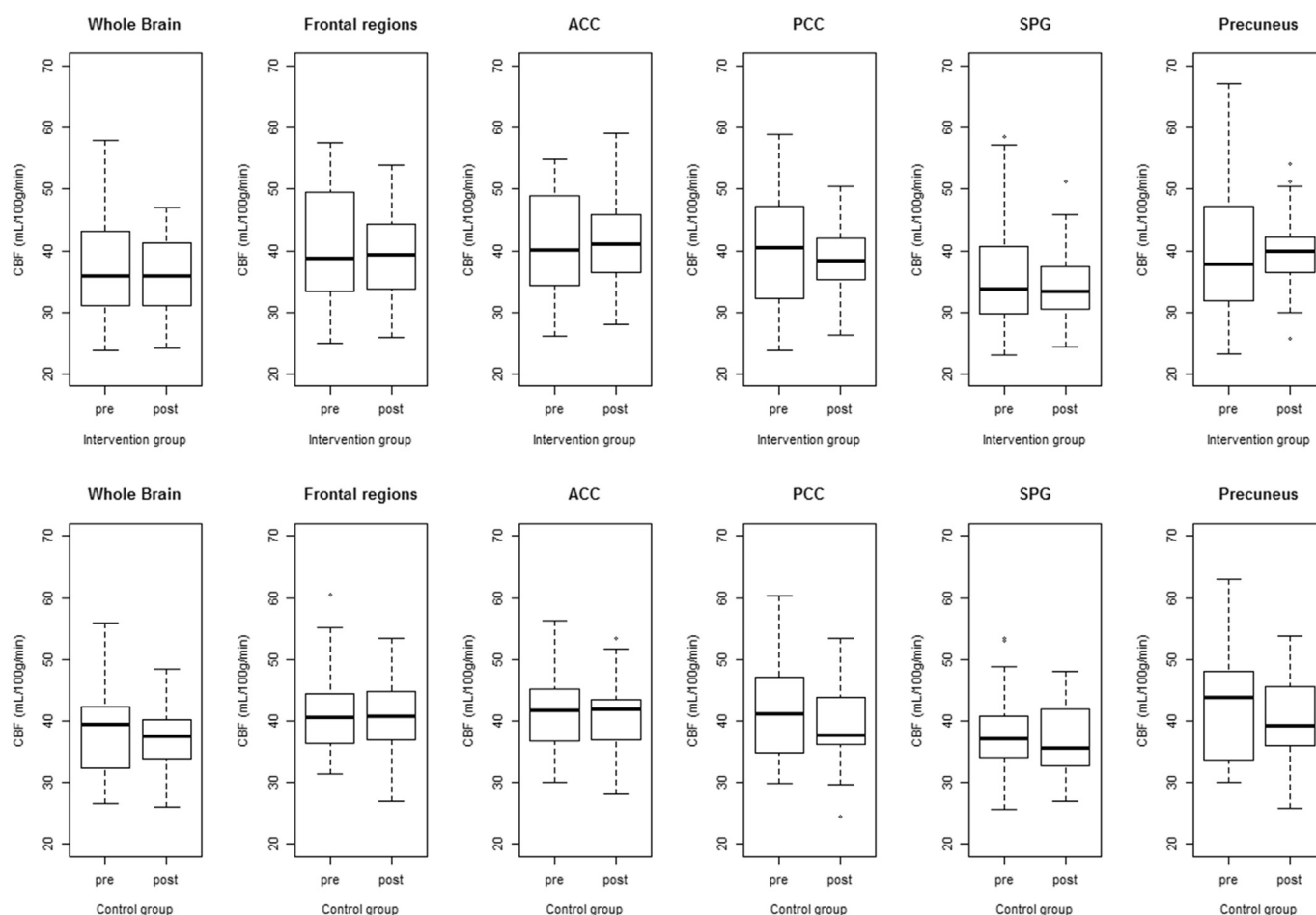


Fig. 2. Change in absolute CBF value (mL/100 g/min) for whole brain, frontal regions, anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), superior parietal gyrus (SPG), and the precuneus.

Table 2

CBF at baseline and at week 16 follow-up visit for the control group and exercise group.

Region	Control group CBF (ml/100 g/min)		Exercise group CBF (ml/100 g/min)		Difference baseline – Follow-up
	Baseline	Follow-up	Baseline	Follow-up	
Whole brain	39 (IQR 32–42)	37 (IQR 34–40)	36 (IQR 31–43)	36 (IQR 31–41)	n.s./n.s.
Frontal regions	41 (IQR 36–44)	41 (IQR 37–45)	39 (IQR 34–49)	39 (IQR 34–44)	n.s./n.s.
ACC	42 (IQR 37–45)	42 (IQR 37–43)	40 (IQR 34–49)	41 (IQR 37–46)	n.s./n.s.
PCC	41 (IQR 35–47)	38 (IQR 36–43)	40 (IQR 33–47)	38 (IQR 36–42)	n.s./n.s.
SPG	37 (IQR 34–41)	36 (IQR 33–42)	34 (IQR 30–41)	33 (IQR 31–37)	n.s./n.s.
Precuneus	44 (IQR 34–48)	39 (IQR 36–46)	38 (IQR 33–46)	40 (IQR 37–42)	n.s./n.s.

ACC = anterior cingulate cortex; PCC = posterior cingulate cortex; SPG = superior parietal gyrus; n.s. = not significant.

selected a priori to monitor the effect of exercise on CBF in AD. The number and location of hypoperfused regions varies among studies, but the precuneus and posterior cingulate cortex are consistently found hypoperfused on ASL MRI in AD (Alsop et al., 2010; Schroeter et al., 2009; Sierra-Marcos, 2017). Both regions were included in the analyses of the current study.

The negative results might be due to mild to moderate AD diagnosis of the participants. The disease may be too advanced to induce any CBF increase, because chronic hypoperfusion is hypothesized to precede neurodegeneration years before symptom onset (Daulatzai, 2017; Hays et al., 2016). Furthermore, hypoperfusion can cause characteristic AD pathology (Koike et al., 2011). This suggests that CBF should be targeted in healthy elderly or MCI patients to prevent or postpone AD pathology, whereas in our study population AD pathology had already manifested. As well, the occurrence of mild small vessel disease as indicated by the WMH volumes in our study may limit ability to increase CBF, because it is also associated with decreased CBF. Several studies have shown an effect of exercise on CBF in healthy elderly (Shi et al., 2016). Several studies have shown an effect of exercise on CBF in healthy elderly. For example, an increase in ACC CBF was found after three months of training, whereas no change in whole brain CBF occurred in healthy adults (57–75 years old) who underwent an exercise intervention comparable to the ADEX trial (Chapman et al., 2013). In comparison, no change in ACC CBF was found in the current study. An increase in hippocampal CBF but no change in ACC CBF was observed in healthy adults (70–85 years old) after 4 months of partially unsupervised exercise (Burdette et al., 2010). The intensity of the training program might also affect study results, as no change in CBF was found in healthy adults (64–78 years old) who underwent an aerobic exercise program of with less training time per session (30–60 min) (Flodin et al., 2017). In addition, a longer training period may be required to see results in patients with advanced disease. Therefore, future studies should consider a longer intervention or patients with less advanced disease.

Cerebral blood flow has been linked to disease severity as measured with the MMSE in MCI and AD patients (Binnewijzend et al., 2013), and a possible cause for the CBF reduction seen in this patient population is amyloid deposition in the cerebral blood vessels (van Osch and M, 2011). Amyloid β is a vasoconstrictor, and may through this reduce CBF (van Osch and M, 2011). Alternatively, the lowered CBF may reflect lower metabolic demand due to tissue damage or, conversely, tissue damage may be caused by lower CBF (Austin et al., 2011). As such, the question of causality remains unanswered (de la Torre, 2004). It is, however, clear that vascular risk factors play an important role in neurodegeneration (de la Torre, 2004). In the current study, vascular risk factors did not differ between the two study arms. Interestingly, a more active lifestyle of APOE-e4 allele carriers has been associated with lower cerebral amyloid β deposition (Head et al., 2012). In the ADEX trial, no effect was found of the 16 week exercise program on amyloid β concentrations in the cerebral spinal fluid (Steen Jensen et al., 2016).

In summary, the results indicate that there may not be an effect of exercise on cerebral blood flow in individuals with mild to moderate

AD. An alternative explanation is that 16 weeks may be too brief for detectable effects with ASL MRI in this relatively small sample.

Disclosures

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